US-PAT-NO: **5447724**

DOCUMENT-IDENTIFIER: US 5447724 A
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TITLE: Medical device polymer

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US Patent No. - PN (1):
5447724

Brief Summary Text - BSTX (8):
Various embodiments of the device may include the following features. The surface-layer incorporates an **elutable** component to enable formation of pore structure in the surface-layer by solubilizing of the **elutable** component by the tissue during exposure. The tissue-exposed portion is a coating covering the surface of the medical device or the device is formed substantially from the tissue-exposed portion. The reservoir and surface-layer are each less than about 100 mils thick, preferably about 2 to 3 mils thick.

Brief Summary Text - BSTX (9):
Embodiments of the device may further include the following. The tissue-exposed portion is constructed for prolonged release of the agent for a period corresponding to the duration of the exposure of the device to blood. The tissue-exposed portion is constructed for release at effective levels for at least about 200 hours. The reservoir is comprised of more than about 30% by weight of the agent, preferably about 40 to 60% by weight of the agent. The reservoir includes a physiologically active **elutable** component. The agent is

selected from an antithrombogenic drug such as heparin, antiplatelet drug such as aspirin, a prostaglandin such as prostacyclin, a thrombolytic drug, such as tPA, urokinase, streptokinase, prourokinase or an antiproliferative drug such as heparin or asteroid such as cortisone, an antirejection drug such as cyclosporin, an antimicrobial drug such as Vancomycin, a growth factor such as epidermal growth factor, platelet growth factor and fibroblast growth factor and an anticalcifying agent such as a diphosphonate. The agent is in particulate form with a particle size about the thickness of the reservoir or less or preferably less than about 10 micron particle size.

Brief Summary Text - BSTX (10):

Embodiments of the device may also include the following. The surface-layer is less than about 20% by weight of the **elutable** component preferably about 10 to 20% by weight of the **elutable** component. The **elutable** component is in colloidal regions and selected from polyethylene oxide, polyethylene glycol, polyethylene oxide/polypropylene oxide copolymers, polyhydroxyethylmethacrylate, polyvinylpyrollidone, and polyacrylamide and its copolymers and liposomes. The polyethylene oxide has a molecular weight of less than about 100,000. The **elutable** component is in particulate form and selected from albumin, dextran, proteins, peptides, polysaccharides, biodegradeable polymers and soluble cellulosics such as hydroxypropyl cellulose. The **elutable** component is a biodegradeable polymer selected from the group consisting of polylactides, polygalactides, polyanhydrides, polyorthoesters and their copolymers. The **elutable** component is a physiologically active agent. The surface-layer incorporates a minor amount of the physiologically active agent prior to exposure to

blood. The **elutable** component creates regions of about 50 microns or less in the surface-layer, preferably, about 10 microns or less or submicron in size.

Brief Summary Text - BSTX (13):

In another aspect, the invention features a medical catheter device for use in blood-containing body lumens formed of a flexible catheter-defining substrate with a blood-exposed coating capable of substantially maintaining the flexibility of the catheter and constructed to release an anticoagulant agent that inhibits the formation of thrombus. The coating is defined by a polymeric surface-layer overlying in a supported manner a polymer defining a reservoir layer. The reservoir layer incorporates the anticoagulant agent to permit substantially free outward release of the agent from the reservoir. The overlying layer incorporates an **elutable** component, soluble in blood to enable formation of pore structure in the surface-layer by solubilizing of the **elutable** component by the blood during exposure. The pore structure defines metering outward passages constructed to control the outward migration of the agent to enable prolonged release of the agent from the surface of the medical device to prevent adverse reaction due to the presence of the device.

Brief Summary Text - BSTX (16):

Embodiments of the method may also feature the following steps. The surface-layer is formed by incorporating into the surface-layer an **elutable** component to enable formation of pore structure defining the passages in the surface-layer by solubilizing of the **elutable** component by the tissue during exposure. The tissue-exposed portion is provided by forming a mixture

including a reservoir polymer and the **elutable** component, forming the reservoir from the mixture, forming a mixture including a surface-layer polymer and the agent and applying the surface-layer mixture to the reservoir layer to form the surface-layer. The surface layer mixture is formed by mixing the surface-layer polymer and the **elutable** component in a solvent and evaporating the solvent to form the reservoir. The mixing involves mixing to suspend particulates or mixing to form a colloidal suspension in the solvent. For colloidal suspensions, the mixing may feature selecting the **elutable** component from polyethylene oxide, polyethylene glycol, polyethylene oxide/polypropylene oxide copolymers, polyhydroxyethyl methacrylate, polyvinylpyrollidone, and polyacrylamide and its copolymers and soluble cellulosics such as hydroxypropyl cellulose, polysaccharides and liposomes. The size and concentration of the **elutable** component is selected to produce a continuous network in the polymer.

Brief Summary Text - BSTX (18):

Embodiments of the method may also include the following. The tissue exposed portion is applied as a coating to the surface of a medical device substrate. The tissue exposed portion is formed to be at least as flexible as the substrate. The device is coated by successively passing portions of the device, without deformation, through the mixtures so that the successive portions are exposed to the mixture for substantially the same time. The tissue exposed portion is formed by thermal methods such as thermal extrusion or molding a mixture of the active agent and the reservoir polymer and/or extrusion or molding of a mixture of the **elutable** component and the surface layer polymer.

Drawing Description Text - DRTX (11):
FIG. 4 is a graph comparing heparin release from a polymer having a PEO **elutable** component according to the invention and a prior art coating.

Drawing Description Text - DRTX (12):
FIG. 5 is a graph comparing the release rate of heparin from a polymer having a dextran **elutable** component according to the invention and a prior art coating.

Detailed Description Text - DETX (4):
The further enlarged cross-sectional view in FIG. 1b depicts the polymer 16 prior to substantial exposure to body fluids such as blood and plasma. The blood-exposed polymer 16 is a coating, e.g., about 4-mils thick, on the catheter substrate material 18 and includes a polymeric surface-layer 20 (about 2 mils thick) which typically, prior to exposure to body fluids, incorporates **elutable** components 22, such as communicating pockets of PEO, that are soluble in body fluids and held in a polymer binder 19 such as polyurethane. A reservoir portion 24 (about 2 mils thick) is bonded (for example, mechanically or chemically) directly to the medical instrument substrate 18 and supports (by mechanical or chemical bonding) the outer layer 20. The reservoir incorporates communicating pockets of the physiologically active agent 26 in a polymer binder 23 which may also be polyurethane.

Detailed Description Text - DETX (5):
Referring now to FIG. 1c, when the polymer 16 is exposed to body fluids, the **elutable** component 22 goes into solution and is removed from the surface-layer

20 forming a porous network 21 of communicating tortuous passageways through which body fluids may migrate, reach the reservoir portion 24 and enable release of the physiologically active agent 26. The released physiologically active agent diffuses through the body fluid in the pores to the surface of the surface-layer where it interacts with the body fluid in the body lumen to inhibit adverse reactions to the presence of the device. As the agent is released over time, pore structure is formed from the communicating pockets in the reservoir portion, forming a porous network in the reservoir so that agent contained in portions of the reservoir away from the surface-layer may also be released.

Detailed Description Text - DETX (6):

Referring now to FIGS. 2-2c, a drug delivery catheter is shown. The catheter 25 which may be, for example, a drug delivery catheter is introduced to the patient's body to a blood vessel 12. Referring to FIGS. 2a and 2b, the catheter 25 is formed entirely from a polymer according to the invention. The polymer has a surface-layer 28 exposed to the body lumen and on the walls of the inner catheter lumen 14, that includes **elutable** material 22. A physiologically active agent is incorporated in the reservoir portion 27 which forms, substantially, the structure of the catheter. As shown in FIG. 2c, after exposure to body fluids, the **elutable** material of the surface-layer dissolves forming a pore structure 21 through which the physiologically active material may migrate from the reservoir portion.

Detailed Description Text - DETX (8):

The medical devices of the invention having release polymers of the

invention enable a gradual, long-time release, on the order of several weeks if desired, of physiologically active agents such as heparin to inhibit adverse reactions to the presence of the medical device. The reservoir portion is formulated to enable substantially free release of the physiologically active agent upon contact with body fluids. In general, the particle size and concentration of active agent are selected to form a communicating network of pockets in the binder of the reservoir. Typically, the particle size is less than about 10 microns, preferably 4 to 8 microns. Particle sizes on the order of the thickness of the reservoir layer may be used, for example, particle sizes of about 50 microns (about 2 mils) for a 2 mil thick reservoir. In some embodiments, high concentrations of active agent, e.g., over 30% by weight are incorporated in the polymer binder. High concentrations are enabled without excessive release rates to the body by the metering effect of the surface-layer, disposed over the reservoir. The reservoir may also include a non-physiologically active **elutable** component to facilitate formation of pore structure and migration of the physiologically active agent, as desired. In general, the reservoir portion contains from about 10 to 90% by weight, preferably 40 to 60% by weight of agent. The agent may be any body-fluid soluble active material or may be a material that is solubilized by the incorporation of pockets containing a solubilizing agent (e.g. PEO) with a less soluble active agent. Agents with beneficial therapeutic effect relating to the prevention of body-rejection reactions such as thrombus formation, platelet aggregration, or cell proliferation may be incorporated. A preferred example is heparin. Other examples include aspirin, prostoglandins such as

prostacyclin, or thrombolytic agents such as tPA, urokinase, streptokinase, prourokinase or antiproliferative agents such as heparin and steroids such as cortisone. Antiproliferative drugs, such as heparin or steroids, may be used, for example, to prevent excessive fibrous tissue formation or contracture that can occur from using devices such as artificial skin or breast prostheses. Additional agents include anti-rejection drugs, such as cyclosporin, to prevent rejection of hybrid artificial organs containing animal cells or tissue; antimicrobial agents such as antibiotics, for example, Vancomycin to prevent infection adjacent to medical devices; peptide or protein drugs such as cell growth factors, for example, epidermal growth factor, platelet derived growth factor or fibroblast growth factor to enhance healthy tissue adjacent to medical devices such as percutaneous connectors; anticalcifying drugs such as diphosphonates to prevent calcification of biomedical materials such as used in heart valves or the artificial heart.

Detailed Description Text - DETX (9):

The surface-layer controls or meters the rate of depletion of the active agent that diffuses from the reservoir portion to the surface-layer through the pores. The surface layer preferably is of substantially uniform thickness and covers substantially completely the underlying reservoir so that no portion of the reservoir is directly exposed to the body. The **elutable** component, incorporated within the surface-layer is an agent that is both biocompatible and soluble in body fluid. The **elutable** component may also be a slightly soluble material which is incorporated within pockets in the reservoir with a highly soluble solubilizing agent. The **elutable** component is present in the

polymer binder in sufficient concentration and of particle size such that
communicating, tortuous channels in the polymer are formed upon exposure to
body fluid. The regions or pockets of **elutable** component are typically from
100 micron to submicron, most preferably less than about 1 micron, in diameter.
Larger particles and higher concentrations of **elutable** component give generally
higher rates of active-agent release. In addition, the surface-layer may be
configured to maintain the integrity and smoothness of the tissue-exposed
portion when the agent has been largely released from the reservoir, leaving a
highly porous polymer binder which might otherwise become a site for platelet
aggregation. Higher molecular weight **elutable** components, such as high
molecular weight PEO, e.g., molecular weight of about 300,000, may cause a
swelling effect in the binder that, while not degrading the performance of the
release polymer, may create a visually detectable physical deformation compared
to a lower molecular weight, PEO, e.g., molecular weight less than around
100,000. A preferred **elutable** component is Carbowax.RTM. 20M (available from
Union Carbide), a PEO with molecular weight of around 20,000.

Detailed Description Text - DETX (10):

In general, the **elutable** component may be colloidal in nature, i.e., it is
in the form of particulates of about 1 micron or less, or, the component may be
particulate in nature where larger, particles, e.g., larger than 1 micron,
preferably less than 10 microns most preferably in the 6 to 8 micron range, are
used. The **elutable** component may also be a biodegradeable component.
Particulate **elutable** agents include, for example, albumin, polyvinylpyrollidone, dextran, **elutable** components include, for example,

polyethylene oxide, polyethylene glycol, polyethylene oxide/polypropylene oxide copolymers, polyhydroxyethyl methacrylate, polyvinylpyrollidone, polyacrylamide and copolymers, soluble celluloses such as hydroxypropyl cellulose and proteins, peptides, polysaccharides and liposomes. The **elutable** components may also be biodegradeable components such as polylactides, polyanhydrides and polyorthoesters and their copolymers. The **elutable** component may also be a physiologically active agent or include a physiologically active agent in addition to non-active components to produce a desired gradual release effect. In particular, it is preferred to incorporate a minor amount, for example, about 2% by weight, active agent such as heparin in the surface-layer to provide antithrombogenic effect upon first exposure of the device to blood, while the **elutable** component dissolves to enable release of the agent from the reservoir (which typically takes 10 to 15 minutes for thin (4 mil) polymer coatings as in FIG. 1).

Detailed Description Text - DETX (17):

For formation of the surface-layer the boat 64 is cleaned of the reservoir portion mixture and filled with a mixture including a solvent, e.g. THF (9 parts) and Pellthane.RTM. (1 part) having the desired amount of **elutable** component. The boat is moved over the catheter and dried, as discussed above to form the surface-layer. Subsequent coats may also be formed.

Detailed Description Text - DETX (19):

Articles might also be formed entirely from the release polymer. In this case, a prepolymer mixture including the desired quantity of heparin is prepared, formed into the desired shape and polymerized. A

prepolymer solution
containing an **elutable** component is next applied over the article and
polymerized to form the surface-layer. Additionally, articles may be formed by
thermal means such as injection molding a mixture of polymer and active agent.
The outer layer may be formed by molding the polymer and **elutable** agent mixture
around the body of the device by insert molding techniques.

Detailed Description Text - DETX (27):
A bulk Carbowax.RTM. solution was prepared by pouring the base
Pellthane.RTM. solution into a clean glass bottle and the required amount of
Carbowax.RTM. flakes (weight of Carbowax.RTM. (grams)=weight of base
solution.times.(0.0168)) to form a solution of about 15 wt % Carbowax.RTM. on
a dry weight basis with Pellthane.RTM.. The mixture was placed in an oven for
four hours at 50.degree..+-.10.degree. C. to facilitate the solvation of the
Carbowax.RTM., shaken for five minutes in a tumbler and allowed to cool for at
least three hours at ambient (20.degree.-25.degree. C.) upon which a
suspension of colloidal Carbowax.RTM. solution was formed as indicated by the
translucent, clouded character of the solution. The solution was shaken for
about 5 minutes to break up aggregated particles as indicated by the absence of
larger white particles (greater than about 10 microns in size). The colloidal
suspension, it is thought, creates submicron regions of **elutable** component in
the surface layer.

Claims Text - CLTX (8):
said outer polymer metering layer having a stable, substantially uniform,
predetermined thickness covering the underlying reservoir so that no portion of
the reservoir is directly exposed to body fluids and

incorporating a
distribution of an **elutable** component which, upon exposure to body fluid,
elutes from said outer polymer metering layer to form a predetermined porous
network capable of exposing said therapeutic agent in said reservoir in said
internal polymer layer to said body fluid,

Claims Text - CLTX (9):
said **elutable** component is selected from the group consisting of
polyethylene oxide, polyethylene glycol, polyethylene oxide/polypropylene oxide
copolymers, polyhydroxyethylmethacrylate,
polyvinylpyrollidone, polyacrylamide
and its copolymers, liposomes, albumin, dextran, proteins, peptides,
polysaccharides, polylactides, polygalactides,
polyanhydrides, polyorthoesters
and their copolymers, and soluble cellulosics,

Claims Text - CLTX (10):
said reservoir defined by said internal polymer layer incorporating said
therapeutic agent in a manner that permits substantially free outward release
of said therapeutic agent from said reservoir into said porous network of said
outer polymer metering layer as said **elutable** component **elutes** from said
polymer metering layer, said predetermined thickness and the concentration and
particle size of said **elutable** component being selected to enable said outer
polymer metering layer to meter the rate of outward migration of the
therapeutic agent from said internal reservoir layer through said outer polymer
metering layer.

Claims Text - CLTX (20):
10. The medical device of claim 1 wherein said reservoir includes a
non-physiologically active **elutable** component.

Claims Text - CLTX (24):
14. The medical device of claim 1 wherein said outer polymer metering layer includes less than about 20% by weight of said **elutable** component.

Claims Text - CLTX (25):
15. The medical device of claim 14 wherein said outer polymer metering layer includes about 10 to 20% by weight of said **elutable** component.

Claims Text - CLTX (26):
16. The medical device of claim 1 wherein said **elutable** component comprises colloidal regions in said surface layer.

Claims Text - CLTX (27):
17. The medical device of claim 16 wherein said **elutable** component colloidal regions are polyethylene oxide.

Claims Text - CLTX (29):
19. The medical device of claim 1 wherein said **elutable** component comprises particulate regions.

Claims Text - CLTX (30):
20. The medical device of claim 1 wherein said **elutable** component includes a physiologically active agent.

Claims Text - CLTX (31):
21. The medical device of claim 1 wherein said **elutable** component includes a minor amount of said physiologically active agent prior to exposure of said exposed surface to said tissue.

Claims Text - CLTX (32):
22. The medical device of claim 1 wherein said **elutable** components create regions of about 50 microns or less in said first polymer metering surface-layer.

Claims Text - CLTX (33):
23. The medical device of claim 22 wherein said **elutable** components create regions about 10 microns or less.

Claims Text - CLTX (34):
24. The medical device of claim 23 wherein said **elutable** components create submicron regions.